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Assessment of cardiac biochemical markers cystatin C and lipoprotein(a) and their relationship with glycemic control in type 2 diabetes mellitus patients

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Abstract

Introduction: Type 2 diabetes mellitus, is one of the predominant health emergencies of this century. Cardiovascular diseases are associated with raised morbidity and mortality in diabetes, contributing to substantial share of community health expenditure. This study was taken up to determine level of cardiac biomarkers cystatin C (CysC) and lipoprotein(a) (Lp(a)) & their association with glycemic control & lipid profile parameters to assess cardiovascular risk profile in type 2 diabetes mellitus.

Materials and methods: This study included 100 type 2 diabetes mellitus patients and 100 apparently healthy controls. Diabetic patients were categorised as good glycemic control (50) - HbA1c ≤ 7.5% and poor glycemic control (50) - HbA1c > 7.5% groups. Biochemical parameters CysC, Lp(a), HbA1c and lipid profile were analysed in all participants.

Results: Lp(a) and CysC were significantly increased in diabetic patients than in controls. CysC, total cholesterol (TC), low density lipoprotein (LDL), TC/HDL, LDL/ high density lipoprotein (HDL) ratio were significantly increased and HDL was decreased in poor glycemic control group than good glycemic control. CysC correlated positively with HbA1c, Lp(a), TC and LDL while negatively with HDL which was statistically significant. Correlation observed between Lp(a) and HbA1c was not significant.

Conclusion: Our study denotes increased cardiovascular disease risk in diabetic patients particularly in those with poor glycemic control. Evaluation of CysC and Lp(a) together, would ameliorate cardiovascular disease (CVD) risk prediction and facilitate appropriate interventions. This study aids in stratification of high-risk diabetic persons for cardiovascular diseases at early asymptomatic phases which will prevent or delay disease advancement and improve clinical outcomes in diabetic patients.

***Keywords**:* diabetes mellitus, cystatin C, lipoprotein(a), glycemic control, dyslipidemia

Introduction

Type 2 diabetes mellitus (T2DM) is an alarming non-communicable metabolic-cum-vascular disease [1]. Diabetes, an "Iceberg" disorder; is a prime threat to worldwide communal health. The global epidemic of diabetes has come to be one of the predominant health emergencies of this centennial, listing amongst the upmost 10 principal causes of death [2]. On the report of International Diabetes Federation, extent of individuals suffering from diabetes was predicted to reach 463 million in 2019, by 2030 cases could amount to 578 million and nearby 2045, more than fifty percent of global community could be afflicted [3]. Diabetes is not an epidemic any longer in India, has changed course towards a pandemic, conferring the dubious distinction of "diabetes capital of the world" [4]. The long-standing continuing hyperglycemia is the hallmark of diabetes. It is accompanied by various metabolic dysregulations

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resulting in adverse macrovascular and microvascular ramifications. These consequences amount to high morbidity and mortality by affecting longevity and quality of life [2, 5]. Accordingly, in 2016 WHO set efforts for sensitization and creating awareness towards diabetes across the globe by theme "Beat Diabetes" [1].

Diabetes has been labelled essentially as equivalent to cardiovascular disease (CVD) [6]. CVD manifestations are reflected two to three decades earlier and diabetics further have two-to-four-times susceptibility of non-fatal cardiovascular events and mortality due to CVD as opposed to general population [7]. The proximate association linking diabetes and CVD strengthens the common soil hypothesis speculated by Stern that these intricate diseases share common genetic and environmental antecedents [8]. However, pathophysiologic mechanisms accounting for this considerably increased CVD risk in diabetes stays obscure [9].

Accordingly, evaluation of numerous biomarkers might reveal pertinent aspects of multifaceted pathogenesis and increased cardiovascular morbidity and mortality in diabetes [7]. Usage of established predictive factors are reasonably robust and put forward the plausibility of improvement by employing newly discovered prominent unconventional indices [10]. This conception encouraged researchers towards expedition of specific indicators which would describe high likelihood of cardiovascular complications among diabetics [6]. Such indices comprise of cystatin C (CysC) and lipoprotein(a) (Lp(a)) amidst other markers. The adoption of these biomarkers would provide long-lasting prognostic models for better cardiac risk projection in diabetes [10].

CysC, a naturally occurring, 13kD endogenous protein refers to cystatin superfamily of cysteine-protease inhibitors [11, 12]. It is constitutively secreted by all nucleated cells and is unaltered by extraneous elements such as age, sex, body mass, nutritional status and inflammation [5, 12]. CysC is especially significant for tissue remodelling [6]. The imbalance of elastolytic activity of cathepsins and their inhibitor CysC stimulates neovascularisation and recruitment of inflammatory cells along with plasma lipid aggregation [11, 13]. Appropriately, increased CysC is precisely linked with inflammation and atherosclerosis impacting cardiovascular system [11].

CysC is a classic, unconventional index reflecting GFR and more definitive surrogate biomarker compared with creatinine to determine worsening renal function in advance [5, 14]. Lately, it has been researched about its role in anticipating new-onset or declining cardiovascular events in diabetic patients [12]. CVD risk increases by 1.2 times with each 1 mg/L rise in CysC levels [15]. Therefore, raised CysC shows a significant influence on accelerated cardiovascular risk profile in diabetes [11]. CysC is a surrogate prognosticative biomarker and can be employed as risk evaluation tool for cardiovascular diseases among diabetics [6, 11].

Lp(a) is heterogeneous macromolecular complex which incorporates structural components of lipoprotein and blood clotting system. It is regarded as being genetic deviant of low-density lipoprotein (LDL) [16]. Lp(a), also entitled as "little rascal" is an emergent potent cardiovascular risk element that is interrelated with diabetes to the same effect [4, 9]. Since Lp(a) mimics plasminogen at molecular level, it inhibits action of this zymogen, triggering off impaired fibrinolysis and thereby, procoagulant condition [4]. Lp(a) is a novel Insulin resistance syndrome risk component, involved in expeditious atherogenesis in diabetes [1]. Studies have stated that Lp(a) value of >50 mg/dl led to 3.5-fold increased risk of adverse cardiac incidents in diabetes than general population. Thus, Lp(a) accelerates cardiovascular risk and can be employed as CVD risk predictor in diabetes mellitus in clinical practice.

The interrelation linking diabetes and cardiovascular disease is significant and has incited screening policies in diabetic patients. These will facilitate potential recognition of high-risk persons who would benefit from aggressive preventive strategies since earlier detection is need of the hour [12]. Presently, considerable efforts are being put together for discovery and validation of unconventional risk indicators. Moreover, cardiac biomarkers like CysC and Lp(a) will contribute novel discrete data that would have huge impact on estimating cardiovascular risk in diabetes apart from conventional risk factors [14].

In perspective of this background conception, present study was taken up to assess the level of cardiac biomarkers CysC and Lp(a) & their correlation with glycemic control & lipid profile indices to assess cardiovascular risk profile in type 2 diabetes mellitus.

Materials and methods

This case-control study involved 100 type 2 diabetes mellitus patients and 100 apparently healthy, age and sex-matched controls. This study was conducted at Government Medical College and Hospital, Aurangabad from 2019 to 2020. We included participants in 30-60 years age category, of either gender and willing to participate in study. We excluded subjects with cardiac, renal and liver diseases, infections, pregnancy, thyroid

disorders, alcoholics, smokers, those on glucocorticoid and lipid lowering therapy. Diabetic cases were under the steady-state condition and were enrolled from diabetic clinic at our hospital. Written informed consent was obtained from all members. Institutional Ethical committee for clinical research approved the study protocol.

T2DM was diagnosed based on American Diabetes Association criteria. Study population was categorised into [17]:

Group I: 100 Controls,

Group II: 50 T2DM patients with HbA1c ≤ 7.5% (Good glycemic control),

Group III: 50 T2DM patients with HbA1c > 7.5% (Poor glycemic control).

Following enrollment, physical and clinical examination was done and anthropometric variables (height, weight, waist and hip circumference) were computed. Fasting blood samples were collected from all participants and analyzed for CysC, Lp(a), HbA1c and lipid profile parameters on XL 640 Fully Automated Biochemistry Analyzer. CysC, Lp(a) and HbA1c were assayed by immunoturbidimetric method using commercial kits from ERBA diagnostics.

Statistical analysis

We used GraphPad Prism software version 7.0 for the data evaluation. Differences in demographic characteristics and biochemical parameters were analysed using one-way analysis of variance (ANOVA) test. Study results obtained were expressed as mean ± standard deviation (SD). Pearson's correlation coefficient was used to study correlation among study variables. P value < 0.05 was considered statistically significant.

Results

100 type 2 diabetic patients and 100 controls in 30-60 years age category were enrolled in this study. Diabetic patients were further divided in two groups according to their glycemic control. CysC and Lp(a) levels were measured in all the participants. CysC value were 0.7 ± 0.15 in controls, 1.46 ± 0.44 in good glycemic control group and 1.57 ± 0.43 in poor glycemic control group (p value < 0.01). Similarly, Lp(a) values were 22.88 ± 6.02, 39.08 ± 15.30 and 43.4 ± 17.44 in these groups respectively (p value < 0.05). Raised CysC as well as Lp(a) in diabetic group showed correlation with lipid profile components denoting proatherogenic scenario in these patients. CysC also showed significant positive correlation with HbA1c signaling that poor glycemic control increases the magnitude of adverse cardiac events in diabetes. However, no effect of glycemic control on Lp(a) levels was noted.

Table 1 shows comparison of demographic characters in studied groups. Age, body mass index (BMI), W/H ratio were significantly increased (p < 0.05) in diabetics compared to controls.

Table 1: Comparison of baseline characteristics in studied groups.

Sr. No.	*Clinical parameters*	*Controls (100)*	*Good glycemic control (50)*	*Poor glycemic control (50)*	*p value*
1.	Age (years)	43.93 ± 6.17	45.78 ± 6.65	54.98 ± 4.53	< 0.05
2.	BMI (Kg/m^2)	24.91 ± 2.19	27.81 ± 2.05	30.17 ± 2.1	< 0.05
3.	W/H Ratio	0.84 ± 0.05	0.87 ± 0.06	0.9 ± 0.06	< 0.05

Table 2 shows comparison of biochemical parameters between studied groups. HbA1c, Lp(a), and CysC were significantly increased in diabetic patients than in controls. Mean values of total cholesterol (TC), low density lipoprotein (LDL), TC/HDL and LDL/ high density lipoprotein (HDL) ratio were significantly increased while HDL was decreased in diabetics than in controls.

Table 2: Comparison of biochemical parameters in studied groups.

Biochemical parameters	*Controls (100)*	*Good glycemic control (50)*	*Poor glycemic control (50)*	*p value*
CysC (mg/L) (0.55-1.15)	0.7 ± 0.15	1.46 ± 0.44	1.57 ± 0.43	< 0.01
Lp(a) (mg/dl) (upto 30)	22.88 ± 6.02	39.08 ± 15.30	43.4 ± 17.44	< 0.05
HbA1c (%) (< 5.7%)	5.16 ± 0.28	6.91 ± 0.44	8.6 ± 0.62	< 0.01
TC (mg/dl) (upto 200)	161.43 ± 12.39	182.48 ± 14.35	195.98 ± 11.31	< 0.05
LDL (mg/dl) (upto 100)	87 ± 12.70	107.66 ± 18.46	126.87 ± 17.82	< 0.05
HDL (mg/dl) (40–60)	49.65 ± 6.62	44.63 ± 6.20	37.5 ± 6.11	< 0.05
TC/HDL	3.31 ± 0.52	4.19 ± 0.80	5.40 ± 1.18	< 0.05
LDL/HDL	1.78 ± 0.43	2.50 ± 0.74	3.54 ± 1.09	< 0.05

When biochemical parameters were compared between good glycemic and poor glycemic control groups (Table 3); CysC, TC, LDL, TC/HDL, LDL/HDL ratio were significantly increased and HDL was decreased in poor glycemic than good glycemic control group. However, Lp(a) level did not differ significantly between two groups, though it was raised in poor glycemic group (p= 0.24).

Table 3: Comparison of biochemical parameters in good glycemic control and poor glycemic control groups.

Biochemical parameters	*Good glycemic control (50)*	*Poor glycemic control (50)*	*p value*
CysC (mg/L) (0.55-1.15)	1.46 ± 0.44	1.57 ± 0.43	< 0.01
Lp(a) (mg/dl) (upto 30)	39.08 ± 15.30	43.4 ± 17.44	0.24
HbA1c (< 5.7 %)	6.91 ± 0.44	8.6 ± 0.62	< 0.01
TC (mg/dl) (Upto 200)	182.48 ± 14.35	195.98 ± 11.31	< 0.05
LDL (mg/dl) (Upto 100)	107.66 ± 18.46	126.87 ± 17.82	< 0.05
HDL (mg/dl) (40 –60)	44.63 ± 6.20	37.5 ± 6.11	< 0.05
TC/HDL	4.19 ± 0.80	5.40 ± 1.18	< 0.01
LDL/HDL	2.50 ± 0.74	3.54 ± 1.09	< 0.01

Table 4, explains correlation of biochemical parameters among diabetics. CysC showed significant positive correlation with HbA1c, Lp(a), TC, LDL, TC/HDL and LDL/HDL ratio while negative correlation with HDL. Lp(a) too correlated positively with CysC, TC, LDL, lipid ratio and negatively with HDL. No significant correlation was found between Lp(a) and HbA1c.

Table 4: Correlation of biochemical parameters within diabetic group.

Biochemical parameters		*CysC*	*Lp(a)*	*HbA1c*	*TC*	*LDL*	*HDL*	*TC/ HDL*	*LDL/ HDL*
CysC	'r' value 'p' value	-	0.56 < 0.05	0.41 < 0.05	0.51 < 0.05	0.45 < 0.05	- 0.38 < 0.05	0.43 < 0.05	0.4 < 0.05
Lp(a)	'r' value 'p' value	0.56 < 0.05	-	0.21	0.59 < 0.05	0.61 < 0.05	- 0.43 < 0.05	0.58 < 0.05	0.52 < 0.05

Discussion

Type 2 diabetes mellitus, a worldwide public health challenge, is expeditiously becoming severe and globe is noticing diabetes pandemic. For past few decades, diabetes status has altered through mild disease of older population to one of the vital causes of morbidity and mortality involving young and middle-aged persons [4]. Cardiovascular diseases are associated with raised morbidity and mortality in diabetes, attributing 75% hospitalizations and 70-80% diabetic deaths [7, 16]. There is altogether high lag time between inception of atherogenesis and initial cardiac incident, which offers an advantage to intervene with preventive strategies [16]. The risk of vascular complications in diabetes can be minimized through timely recognition, while irreversible damage has not occurred and appropriate therapy will become effectual [14]. In spite of addressing conventional markers like lipid profile for risk assessment, substantial number of diabetics still keep on to suffer from adverse cardiovascular events. This prompts researchers to explore for novel biomarkers which might deal with residual cardiac risk and hold prognostic impact in these subsets of patients [16]. Employing unconventional, complementing markers such as CysC and Lp(a) seems to be interesting in this perspective. Evaluation of these biomarkers potentially allows early recognition of diabetics with high probability of cardiovascular complications for timely intervention [7].

In present study, diabetic patients represented considerably high CysC levels compared to non-diabetics. It was increased within poor glycemic control group in comparison with good glycemic control and difference was statistically significant. In addition, positive correlation of CysC with HbA1c, lipid profile variables like TC, LDL and lipoprotein ratios while negative correlation with HDL was observed in diabetics. This is in consonance with work of Sumantara [11], Das [12] and Senghoret [13] which depicted correlation of raised CysC with insulin resistance and inflammation, thereby rationalizing the role of high CysC in intensifying CVD risk in diabetes [10].

CysC, a classic, definitive index for renal function assessment, is currently emerging as potential measure of CVD risk projection and is linked with adverse cardiovascular incidents in diabetes [5, 13]. As CysC has key regulatory role in extracellular compartment,

even a small rise in CysC might potentially have serious impact on vascular endothelial homeostasis [16]. During atherogenesis, local imbalance between CysC and cysteine proteases develops while raised CysC promotes plaque vulnerability and progression to atherosclerosis by modulating inflammation and thus eventually affecting cardiovascular system [14].

Therefore, CysC is a classic biochemical marker to estimate CVD risk among diabetics and it could complement currently available traditional markers. In addition, probability of untoward cardiovascular events would be increased with poor glycemic control because glycemic regulation influences CysC concentration. Subsequently, elevated CysC will be promising in the evaluation of proatherogenic state in diabetes and may be interpreted as cardiovascular risk predictor.

In our study, Lp(a) was significantly increased in diabetic patients than in controls. It was relatively higher in poor glycemic control group than good glycemic control but the difference was statistically nonsignificant. Lp(a) did not show any correlation with HbA1c among diabetics implying no effect of glycemic control on Lp(a) levels. Similar outcomes were stated [1, 17-19] that Lp(a) could be contemplated as an independent risk element for CVD in diabetic patients.

Long-standing sustained hyperinsulinemia together with hyperglycemia among diabetics is linked with glycosylation of several proteins in body. Glycosylation lengthens half-life of lipoproteins with reduced apo B-100 clearance bringing about raised Lp(a) in diabetes [1, 9]. Lack of Lp(a) and HbA1c correlation might be owing to lesser influence of glycosylation on Lp(a) levels than genetical determinants [18]. Nevertheless, Elsayed [3] observed decreased Lp(a) in diabetics than in controls and stated that insulin disrupts apo(a) function in hepatocytes and glycosylation increases apo(a) molecular size, effecting lower Lp(a) in diabetes. [16].

Presently, Lp(a) is coming out as robust and independent predictor of adverse cardiac events in diabetes. Raised Lp(a) accords genetical predisposition to CVD and is potentially one of the links to expedited atherogenesis among diabetics [18]. Lp(a) mimics LDL and has potential to undergo oxidation [4]. Lp(a) increases oxidative stress, becomes proinflammatory and atherogenic in high concentrations [20]. Raised Lp(a) in diabetics is indicative of accelerated vascular risk advancing to prospective cardiovascular complications and associated morbidity and mortality.

Lp(a) demonstrated significant positive correlation with TC, LDL, TC/HDL, LDL/HDL ratio while negative correlation with HDL among diabetics in this study. Diabetic patients with poor glycemic control demonstrated remarkable rise in TC, LDL and lipid ratios whilst decrease in HDL in comparison with good glycemic control. Consequently, magnitude of adverse cardiovascular events in diabetes increases with raised HbA1c levels. Consistent results were elicited by Kavitha [1], Pujar [4] and Kachhawa [21] signifying proatherogenic status in this group. Lipid ratios have been stated as being greatly sensitive in reflecting atherogenic risk relative to isolated lipid parameters and could be employed as guide for aggressive therapeutical approach.

Our study demonstrated positive correlation between CysC and Lp(a), supported by Lee [22], Guangming [23] and Park. [24] This suggests that combined evaluation of Lp(a) and CysC has beneficial effects towards timely diagnosis, treatment and prognosis of CVD in diabetes. Thus, increase in both CysC and Lp(a) amongst diabetics in this study not merely subjects them towards an accelerated risk of adverse cardiovascular events but also negatively impacts prognosis of these patients subsequent to such events.

In present-day strategies of global risk evaluation, lipid profile is the only blood test usually advised in all setups. Recent studies have proposed complementary predictive significance of multiple biomarkers approach to enhance CVD risk prognostication in diabetes, as every marker exhibits particular dimensions of the risk. Composite assessment of CysC and Lp(a) besides traditional lipid profile holds potential to improve cardiovascular risk prediction. Besides, earlier meticulous control of glycemic status in diabetes is critical to prevent cardiac complications. This strengthens the conception that glycemic control might have lasting impact on clinical events in diabetes. On this account, measuring serum CysC and Lp(a) concentration and intending for good glycemic control in diabetes mellitus will expedite timely intervention strategies, thereby intercepting further cardiac complications.

The study was a single centric study, conducted on comparably small sample size. Hence, large-scale follow-up research is advised on large number of patients aimed at extensive analysis of CysC and Lp(a) in diabetes mellitus subjects for cardiovascular risk prediction.

Conclusion

Periodical evaluation of cardiovascular function is significant aspect of diabetic care in order to implement timely preventative measures. Cardiovascular risk profiling and prognosis in diabetes might potentially

be improved with attainment of good glycemic control along with CysC and Lp(a) estimation. This study aids in stratification of high-risk diabetic persons for cardiovascular diseases at early asymptomatic phases which will prevent or delay disease advancement. Moreover, sequential measurements of these biomarkers can be applied as benchmark for effective novel therapeutic approach and also to contribute further prognosticative data for risk evaluation and improved clinical outcomes in diabetes mellitus patients.

Conflicts of interest

Authors declare no conflicts of interest.

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